REMARKS

Claims 1-33 are pending. Claims 1-26, 29, 30, and 32 are currently under examination. Claims 3, 6-10, 15, 17, 18, 20-22, 24, 25 and 27-29 are cancelled. Claims 31 and 33 are withdrawn, however, Applicants request reconsideration of claim 31 to be included in the elected Group and rejoinder of claim 33. Claims 1, 2, 4, 5, 11-14, 16, 19, and 21-23, 26 and 31 have been amended for clarity. Claims 1, 2, 4, 5, 11-14, 16, 19, 21-23, 26, and 30-32 are currently pending. No new matter has been added. Inventorship of the claims remains the same. Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications. Reconsideration in light of the following remarks is respectfully requested.

Restriction Requirement

Applicants thank the Examiner for her inclusion of claims 2, 4, 12, 14, 17, 19, 22 and 24 into the elected Group.

Applicant requests that the Examiner reconsider the newly amended Claim 31, which deletes the expression "and fusion of said variant protein to another entity", which the Examiner stated, "does not read on the elected variants". Without admitting the propriety of the rejection, Applicants now believe that amended claim 31 falls within the elected claim set and respectfully requests that Claim 31 be included in the elected group.

Claim Rejections - 35 USC 112, first paragraph (enablement)

The Examiner has rejected claims 1-26, 29, 30 and 32 under 35 USC 112, first paragraph, for lacking enablement for a variant protein. Claims 3, 6-10, 15, 17, 18, 20-22, 24, 25 and 29 are cancelled. Claims 1, 2, 4, 5, 11-14, 16, 19, and 21-23, 26 and 31 have been amended for clarity pursuant to the Examiner's suggestion.

The Applicants assume that the "how to make" component of §112, first paragraph is not in question; it appears that the Examiner is taking issue with the "how to use" component of the requirement. The Examiner states that Claim 32 has utility, but states that Claim 32 is not enabled, and states that the cited case law is directed to utility and not enablement. However, the Applicants note that the two requirements are intertwined; in fact, the M.P.E.P. cites utility case law as support for the "how to use" section of 112. See M.P.E.P. §2164.02, citing *In re Brana*.

Essentially, the Examiner's position appears to be that the showing that Applicants' compounds have activity in an *in vitro* assay is insufficient, despite industry acceptance of the assay as correlative to therapeutic efficacy.

Applicants respectfully draw the Examiner's attention to M.P.E.P. §2164.02:

> The issue of "correlation" is related to the issue of the presence or absenc eof woking examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or claimed method of use. . . . In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition.

In the present case, the Applicants have shown that the claimed compounds block osteoclastogenesis, using a RAW264.7 cell model. Osteoclasts function to break down bone; compounds that inhibit osteoclastogenesis serve to increase bone density.

T Federal Circuit requires only a reasonable correlation between an *in vitro* assay and *in vivo* activity to demonstrate therapeutic utility. Applicant has disclosed *in vitro* assay results of the biological activity of the RANKL variants of the present invention. As argued previously, it is well known in the art that a correlation exists between RANKL inhibition and therapeutic efficacy. Applicant contends that the present compounds, shown to be RANKL inhibitors, thus are sufficiently enabled under § 112, first paragraph.

Applicants previously cited a number of references which indicate that the art recognizes that RANKL inhibitors have therapeutic uses. McClung (previously cited) shows that Denosumab (a human monoclonal antibody that blocks the interaction of RANKL and RANK) has therapeutic efficacy. The Examiner states that McClung is not determinative because they show in vivo data. It is precisely this correlation on which the Applicants rely. Similarly, the citation of Wang (previously cited) shows that RANKL inhibitors, as first tested in RAW264.7 cells, result in in vivo efficacy.

Thus, Applicants submit that the art recognizes that RANKL inhibition, as measured in *in vitro* assays, has a reasonable correlation to therapeutic efficacy. Since proteins affecting RANKL binding reasonably correlate such proteins with a pharmacological and therapeutic effect, a skilled artisan would reasonably extrapolate the results known in the art to the presently claimed invention. Thus, no undue experimentation would be needed to practice the invention of claim 32.

In light of the above arguments, Applicants request that the Examiner withdraw the rejections.

Claim Objections

Applicants have corrected the typographical errors in claims 1, 11, 12, and 16 and request that the objection be withdrawn. Claims 17, 21, 22, and 25 are cancelled.

Rejoinder

Applicants believe that the case is now in condition for allowance and respectfully requests rejoinder of claim 33.

CONCLUSION

Applicants believe the claims are in a condition for allowance. Early notification thereof is respectfully requested. The Examiner is invited to call the undersigned at 415.442.1000 to resolve any questions. Although Applicants do not believe any additional fees are required, the Commissioner is authorized to charge any additional fees that may be required or to credit any overpayment to Deposit Account No. 50-0310 (Docket No. 067461-5105-US01).

Respectfully submitted,

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